REMARKS

I. Status of the Claims

Claims 1-56 were originally filed. As the result of a restriction requirement, claims 14, 16-22, and 25-56 were withdrawn from consideration. Subsequently, claims 3-5 and 8-12 as well as all withdrawn claims were canceled. Upon entry of the present amendment, claim 13 is canceled. Claim 1 is amended to recite "an amino acid sequence that has greater than 80% identity to SEQ ID NO:5," which finds support in the specification, *e.g.*, on page 44, line 30, to page 45, line 2. Claims 2, 6, and 7 are further amended to delete recitation of the non-elected species (SEQ ID NO:3 or 4). Claim 24 is amended to clarify that the claimed subject matter is an "isolated" host cell, support for which can be found, *e.g.*, on page 49, lines 30-31, of the specification, where transfection of cells *in vitro* using the claimed nucleic acid is mentioned. No new matter is introduced by the present amendment.

II. Amendment to Specification

The specification is amended to address the Examiner's objection for incomplete priority information. The amendment adds no new matter.

III. Claim Objections

Claims 1, 2, 6, 7, 13, 23, and 24 were objected to for covering non-elected subject matter. Applicants submit that the present amendment fully addresses this objection. Claims 6 and 7 were also objected to for depending from rejected claims. Since all claim rejections are addressed in view of the claim amendment and discussions below, Applicants submit that the objection to claims 6 and 7 is obviated.

IV. Claim Rejections

A. 35 U.S.C. §112, First Paragraph: Written Description

Claims 1, 2, 13, 23, and 24 were rejected under 35 U.S.C. §112, first paragraph, for alleged failure to meet the written description requirement. Applicants respectfully traverse the rejection, particularly in light of the present amendment.

Possession of claimed invention may be shown by a variety of descriptive means, including words, structure, figures, diagrams, and formulas. MPEP §2163 I. Case law provides more specific guidance in setting the standard for written description.

The amended claims are directed to an isolated nucleic acid encoding a beta subunit of a potassium channel. The beta subunit has the following properties: it can form a Slo channel with at least one alpha subunit polypeptide; and it comprises an amino acid sequence with a greater than 80% identity to SEQ ID NO:5. The amended claims fully comply with the requirements for written description of a chemical genus as set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). As described by the Federal Circuit in *Lilly*, "[a] description of a genus of cDNAs may be achieved by means of . . . a recitation of structural features common to the members of the genus . . . ." *Lilly*, 43 USPQ2d at 1406. Furthermore, the court in *Fiers v. Revel* stated that an adequate written description "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Fiers*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993).

On the other hand, proper description of functional features of a claimed invention can play an important role in satisfying the written description requirement. The Federal Circuit recently stated that "*Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385, 1398 (Fed. Cir. 2003).

With regard to the claimed nucleic acids, pending claims set forth both functional features, *e.g.*, encoding a beta subunit of a potassium channel that can form a Slo potassium channel with at least one alpha subunit, and structural features, *e.g.*, comprising an amino acid sequence at least 80% identical to SEQ ID NO:5.

The percentage sequence identity of an amino acid sequence to a reference sequence is a physical/structural property of the nucleic acid encoding the amino acid sequence, because the amino acid sequence is determined by the primary nucleotide sequence of the

nucleic acid. Thus, pending claims set forth commonly shared structural features of the claimed nucleic acids.

Commonly shared functional features of the claimed nucleic acids are also provided: each encodes a beta subunit of a potassium channel that is capable of forming a Slo potassium channel with at least one alpha subunit. These functional features can be readily tested by one of ordinary skill in the art using well-established, routinely practiced techniques as well as according to the teaching of the present specification (*see, e.g.*, page 42, lines 25-32, and Examples I-III).

Thus, both structural and functional features commonly shared by the claimed genus have been described in detail, which "clearly allow persons of ordinary skill in the art to recognize that [the applicant] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). Such description is consistent with the standards set forth in both *Lilly* and *Amgen*..

Based on the analysis under *Lilly* and *Amgen* provided above, Applicants believe the claimed invention within the current claim scope is properly described by the specification under 35 U.S.C. §112 first paragraph. As such, the withdrawal of written description rejection is respectfully requested.

B. 35 U.S.C. §112, First Paragraph: Enablement

Claims 1, 2, 13, 23, and 24 were rejected under 35 U.S.C. §112, first paragraph, for alleged failure to meet the enablement requirement. Applicants respectfully traverse the rejection, particularly in light of the present amendment.

A claimed invention is enabled when the disclosure allows one of ordinary skill in the art to make and use the invention without undue experimentation. MPEP §2164.01. The test for enablement, as set forth in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), requires the consideration of multiple factors: the breadth of the claims; the nature of the invention; the state of the prior art; the level of predictability in the art; the amount of direction provided by the

inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In the present case, the claims are directed to an isolated nucleic acid encoding a BK beta subunit of a potassium channel with well-defined structures and readily testable functional features. The specification contains ample directions to practice the invention, such as methods of cloning the coding sequence for the claimed potassium channel subunit (*see, e.g.*, page 27, line 19, to page 30, line 22, and Examples I-III), expression of the beta channel subunit (*see, e.g.*, page 30, line 25, to page 32, line 34), purification of the beta subunit (*see, e.g.*, page 33, line 2, to page 35, line 28), immunological detection of the beta subunit (*see, e.g.*, page 35, line 31, to page 42, line 20), and electrophysiological assays for studying the ion channel functions (*see, e.g.*, page 42, line 25, to page 45, line 15). The level of technical sophistication is high in the art, and the BK potassium channel beta subunit variants can be readily tested according to the methods commonly used by those skilled in the art or the methods taught by the specification (such as nucleic acid or amino acid sequence comparison and functional assays for Slo potassium channels) to eliminate inoperable embodiments. MPEP §2164.01 states, complex experimentation is not necessarily undue, if the art typically engages in such experimentation. In the present case, although some experimentation may be involved to practice the claimed invention using embodiments other than those specifically described in the application, such experimentation utilizes well-established techniques and is the type routinely conducted in the art. Thus, the experimentation does not constitute undue experimentation.

The pending claims specify that the beta subunit encoded by the claimed nucleic acid has at least 80% identity to a reference amino acid sequence, SEQ ID NO:5. The level of identity required by the claims is intended to encompass other naturally occurring variants and alleles of human BK beta 4 that have the same function as a polypeptide consisting of SEQ ID NO:5, as well as closely related orthologs that have essentially the same function. In addition, this level of identity is intended to encompass variants engineered for ease of experimental manipulation--for example, variants that include amino acids that can be modified so that the polypeptide can be more easily purified.

Methods for determining percent identity are disclosed in the specification and are also well known to those of skill in molecular biology. These elements therefore provide adequate guidance for routine identification of the polypeptides of the invention. In addition, the pending claims specify that the polypeptide is capable of forming, with an alpha subunit, a Slo potassium channel. Therefore, the claimed nucleic acid can be identified based on the functionality of the polypeptide it encodes. The level of ordinary skill in the art of biotechnology is considered very high. Therefore, given the high degree of sequence identity required in the claims (at least 80%) and the assays provided, which allows one of skill in the art to verify whether a particular polypeptide has the ability to form a Slo potassium channel with an alpha subunit, Applicants respectfully submit that undue experimentation is not required to practice the claimed invention.

As already mentioned above, some routine experimentation is tolerated by the enablement requirement. Given the high level of skill in the field of biotechnology, using the present invention the skilled practitioner would attempt to retain, not abolish, the functionality of the polypeptide by suitable changes in the sequences--for example, the skilled practitioner would avoid inserting a run of 10 prolines in the sequence, which are known to alter the secondary structure of a polypeptide by creating bends or kinks. As described in the specification on page 17, line 22, to page 18, line 26, conservative amino acid substitutions are well known, where one amino acid is substituted by a structurally similar amino acid. The specification also lists a table of conservative amino acid substitutions. Moreover, BK beta 4 is a beta subunit of a Slo potassium channel that belongs to a family of polypeptides whose structure is well-characterized; one of skill in the art would know how to avoid abolishing the function of the polypeptide. Any inoperable embodiments resulted from modification of a functional polypeptide can be easily identified in a functional assay and excluded from the claim scope.

Finally, regarding the issue of enablement for nucleic acids and polypeptide sequences, where a large number of possible embodiments exist, the PTO has provided express guidelines for examination. As set forth in the MPEP § 2164.08, a rejection of claims such as

those in the present application for undue breadth is inappropriate where one of skill could readily determine any one of the claimed embodiments.

This standard is further explained in the "Training Materials for Examining Patent Applications with respect to 35 U.S.C. §112, first paragraph – Enablement Chemical/Biotechnological Applications," section III.A.2.b.i(c). In the guidelines, the PTO specifically answers the question regarding scope of a nucleic acid composition claim left open by the Federal Circuit in *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995). The claims at issue in *Deuel* were directed to any DNA encoding a specific amino acid sequence. Thus, a great number of nucleic acids were within the scope of the claims. In fact, the number was so great that a listing of all possible DNAs encoding the protein was a practical impossibility.

In the guidelines, the PTO addresses this issue, explaining that "even though a listing of all possible DNAs which encode a given protein is a practical impossibility due to the enormous number of such nucleic acids, any particular sequence can be written by one of skill given the disclosure and the sequence can be ordered from a company which synthesizes DNA." In this manner, one of skill in the art can readily determine any one of the embodiments. The PTO concludes that scope rejections such as the one hypothesized in *Deuel* should not be advanced.

In the present application, one of skill in the art only needs to identify polypeptides, using well-know sequence algorithms, that have at least 80% identity to a reference sequence. Although many such nucleic acids are possible, one of skill can readily determine, one by one, any particular potassium channel beta subunit polypeptide, without undue experimentation. Furthermore, one of skill can use the assays described in the application to test the required functionality and easily determine if the polypeptide falls within the scope of the claims. Thus, in the present application the skilled artisan can readily, with only routine experimentation, make and test any particular nucleic acid within the claim scope.

The assays described in the specification, coupled with methodology well known to those of skill in the art, therefore demonstrate that making a Slo channel beta subunit and confirming its functionality is routine. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The Examiner specifically rejected claim 24 for alleged lack of enablement, asserting that since a host cell transfected with an expression vector comprising the claimed nucleic acid could be interpreted as a cell in a multicell transgenic organism, and since transgenic organisms are difficult to make the chance of success is unpredictable, undue experimentation would be required for one to produce a transgenic organism having acquired the claimed nucleic acid, a claim directed to a host cell comprising the claimed gene as a transgene is therefore not enabled. Applicants cannot agree with the Examiner.

First of all, claim 24 has been amended to recite an "isolated" host cell, which does not encompass cells that are a part of a transgenic organism. The Examiner's reasoning for the enablement rejection thus does not apply to the amended claims.

Secondly, even if claim 24 had not been amended and were directed to a host cell transfected with an expression vector comprising the claimed nucleic acid, which encodes for a beta subunit of a potassium channel, sufficient enablement would still be found because such host cell would have at least one enabled use. The specification teaches various uses of the host cell. For example, on page 5, lines 3-12, the specification teaches the use of a host cell expressing the claimed BK beta subunit of a potassium channel for identification of a compound capable of modulating ion flux through the potassium channel. On the other hand, on page 54, lines 4-26, the specification teaches the introduction of the claimed nucleic acid into certain cells for therapeutic purposes. Thus, the claimed host cells have multiple uses and at least some of the uses (*e.g.*, use of cultured cells expressing a claimed BK beta subunit following a transfection for the purpose of screening for compounds modulating potassium channel activity) are immediately apparent to those skilled in the art. These uses are also fully enabled immediately upon the disclosure of the coding sequences of the claimed BK beta subunit, given the high level of technical sophistication in the relevant art of molecular biology.

MPEP § 2164.01(c) describes the enablement standard for compound and composition claims as follows:

> [W]hen a compound or composition claim is not limited by a recited use, any enabled use that would reasonable correlate with the entire scope of that claim is sufficient to preclude a

> rejection for nonenablement based on how to use. . . . In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

Under this standard, the host cell of claim 24 would be sufficiently enabled even without the present amendment.

As such, Applicants respectfully submit that the enablement rejection of claim 24 on this ground is improper and should be withdrawn.

In summary, analysis of the *Wands* factors and the facts in the present case indicates proper enablement of the claimed invention. The Examiner's specific concerns regarding claim 24 are also addressed. Applicants therefore respectfully request the withdrawal of the enablement rejection.

C. 35 U.S.C. §102

Claims 1, 2, 13, 23, and 24 were rejected under 35 U.S.C. §102(a) for alleged anticipation by Wallner *et al.* (*Proc. Natl. Acad. Sci. USA*, 1999, **96**:4137-4142). Applicants respectfully traverse the rejection.

The present application, a 35 U.S.C. §371 of PCT/US00/04441, claims priority to USSN 60/121,224, filed February 23, 1999, and USSN 60/163,367, filed November 3, 1999. A review of the sequence listing in the earlier filing, USSN 60/121,224, confirms that SEQ ID NOs:5 and 6 are entitled to the earlier filing date of February 23, 1999. In contrast, the Wallner *et al.* reference was published in March 1999, as indicated in the upper left corner on page 4137 of the reference. The attached copy of a date-stamped page in the March 30, 1999, issue of *Proceedings of the National Academy of Sciences of the United States of America* (volume 96, pages 3331-4214) further confirms that the Wallner reference was not publicly available until about April 26, 1999 (see Exhibit I). Therefore, this reference is not a prior art reference and cannot be relied upon as the basis of a §102(a) rejection. The withdrawal of the anticipation rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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Attachment (Exhibit I: copy of date-stamped page in the March 30, 1999, issue of PNAS)
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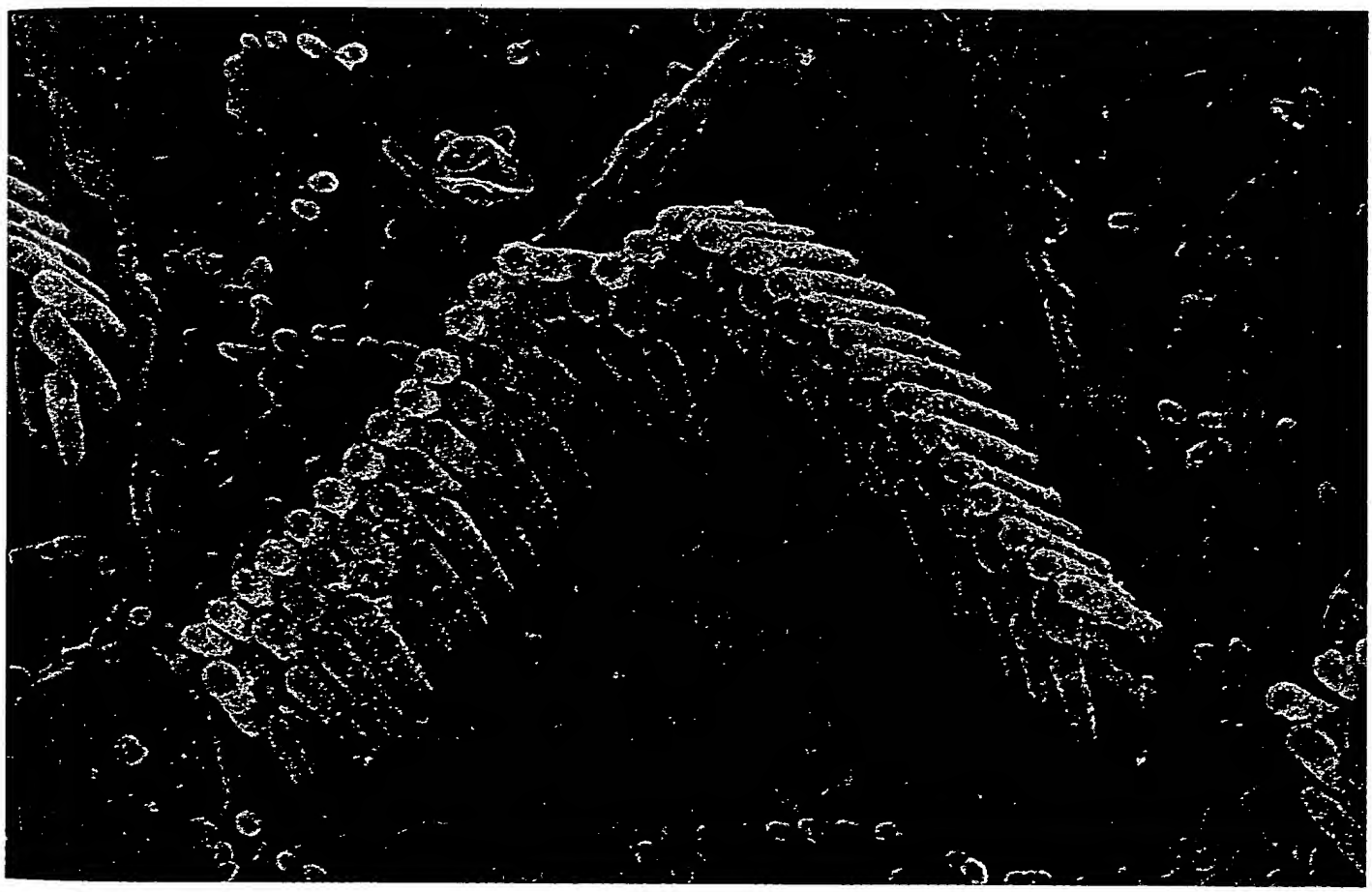

Retaining proliferative capacity in the cochlea
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Ca^{2+}: Blocker and modulator of pore activity
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